#12

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of: Curtis, Rory A.J.

Serial No.: 09/587,111

Filed: June 2, 2000

For: NOVEL MEMBERS OF THE CAPSAICIN/VANILLOID RECEPTOR FAMILY OF PROTEINS AND USES THEREOF

Attorney Docket No.: MNI-062CP2DV1

OIPE JC102 MAY 12 2003 PATENT & TRADEMARK OFFICE

Group Art Unit: 1646

Examiner: Ulm, J. D.

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Commissioner for Patents
Box AF
Washington, D.C. 20231

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I hereby certify that this correspondence is being facsimile transmitted to the Commissioner for Patents, Box AF, Washington, D.C. 20231 on the date set forth below.

4/11/03
Date of Signature

By: Maria Laccotripe Zacharakis

Maria Laccotripe Zacharakis, Ph.D.
Attorney for Applicant
Limited Recognition Under 37 C.F.R. 10.9(b)

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DECLARATION PURSUANT TO 37 CFR §1.131

Dear Sir:

I, Rory A.J. Curtis, a citizen of the United Kingdom, residing at 78 Hardwick Road, Ashland, Massachusetts 01721 hereby declare as follows:

(1) I am the inventor of the subject matter described and claimed in the above-identified application.

(2) Prior to January 22, 1999, the invention described and claimed in the above-referenced patent application was completed in this country, as evidenced by the following:

(a) Prior to January 22, 1999 I had completed the sequencing of the full length human VR-2 (SEQ ID NO:5) as evidenced by copies of the assembled contig map and the complete sequence of SEQ ID NO:5 derived from the contig map. The contig map and sequence print-out are submitted herewith as Exhibits A and B, respectively.

(b) Prior to January 22, 1999 I had determined that the polypeptide of SEQ ID NO:5 was a vanilloid receptor based on the results of a blast search using the amino acid sequence of SEQ ID NO:5. The top hit in this blast search analysis is rat vanilloid receptor 1 (VR-1; accession number AF029310). Based on the percent identity and percent similarity between the polypeptide of SEQ ID NO:5 and rat VR-1, and the fact that rat VR-1 was the top hit in the blast search analysis I determined that the polypeptide of SEQ ID NO:5 was a vanilloid receptor. The results of the blast search analysis are submitted herewith as Exhibit C.

(c) Prior to January 22, 1999, I had determined that the polypeptide of SEQ ID NO:5 represents a unique target for pain and that it may be responsible for hypersensitivity in chronic neuropathic pain, as evidenced by a copy of the "Qualified Target Summary Sheet" generated for this molecule. The Qualified Target Summary Sheet is submitted herewith as Exhibit D.

(d) According to my routine practice, immediately after identifying the polypeptide of SEQ ID NO:5 as a vanilloid receptor (hVR-2) associated with pain and classifying it as a Qualified Target, I contemplated routine uses of this molecule such as: (i) use of the molecule in screening assays to identify modulators of the vanilloid receptor or (ii) use of this molecule in the diagnosis of conditions/diseases associated with, for example, aberrant vanilloid receptor (hVR-2) nucleic acid expression or activity, *e.g.*, pain disorders, as evidenced by a copy of the "Qualified Target Summary Sheet" generated for this molecule.

(e) The dates deleted from the contig map (Exhibit A), the sequence print-out (Exhibit B), the blast search results (Exhibit C), and the Qualified Target Summary (Exhibit D) are prior to January 22, 1999.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this Application for Patent or any patent issuing thereon.

Rory Curtis
Rory A.J. Curtis, Ph.D.

4/10/2003
Date

Exhibit A

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Sequencher™ "21e11racefinal"

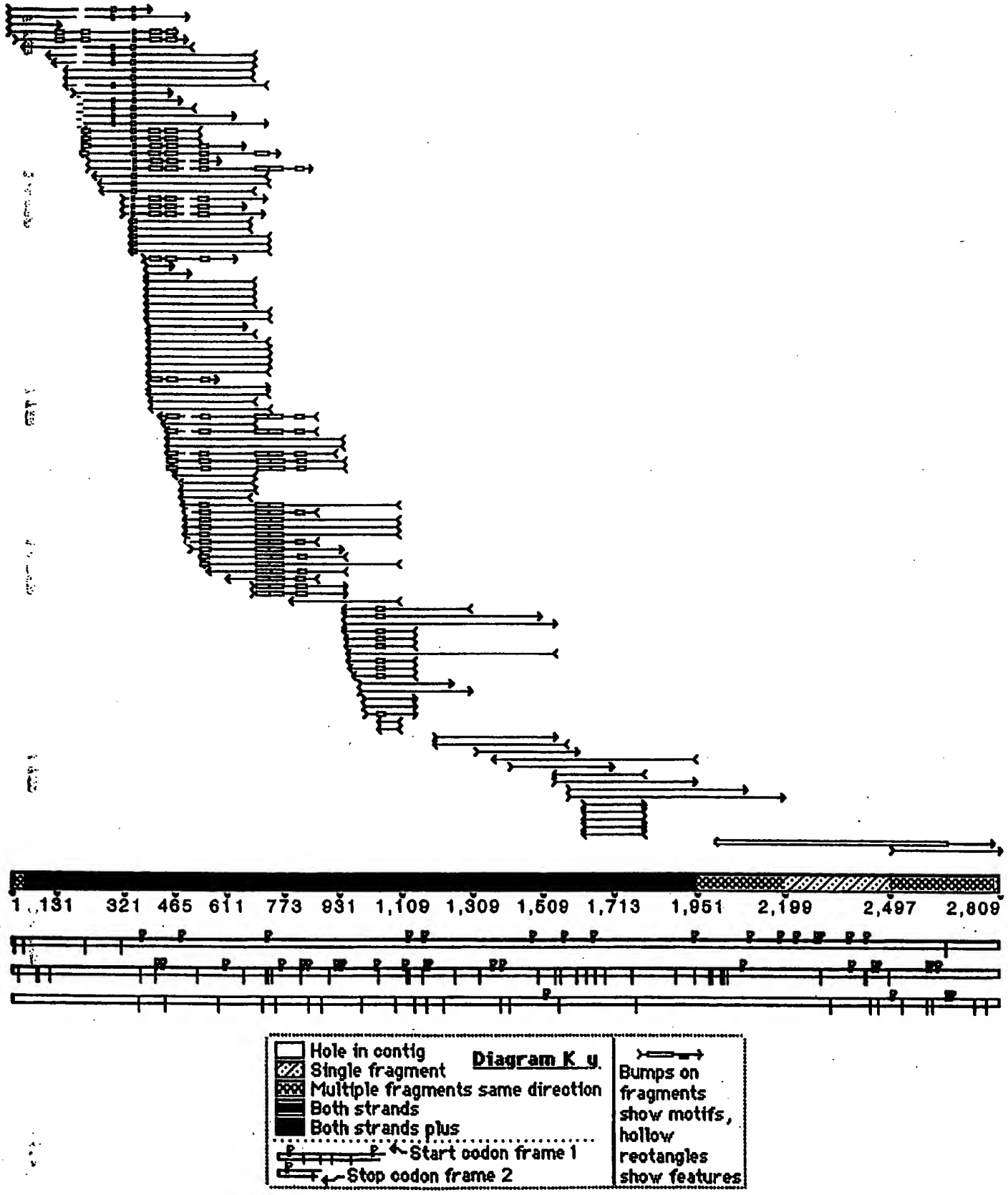

Exhibit B

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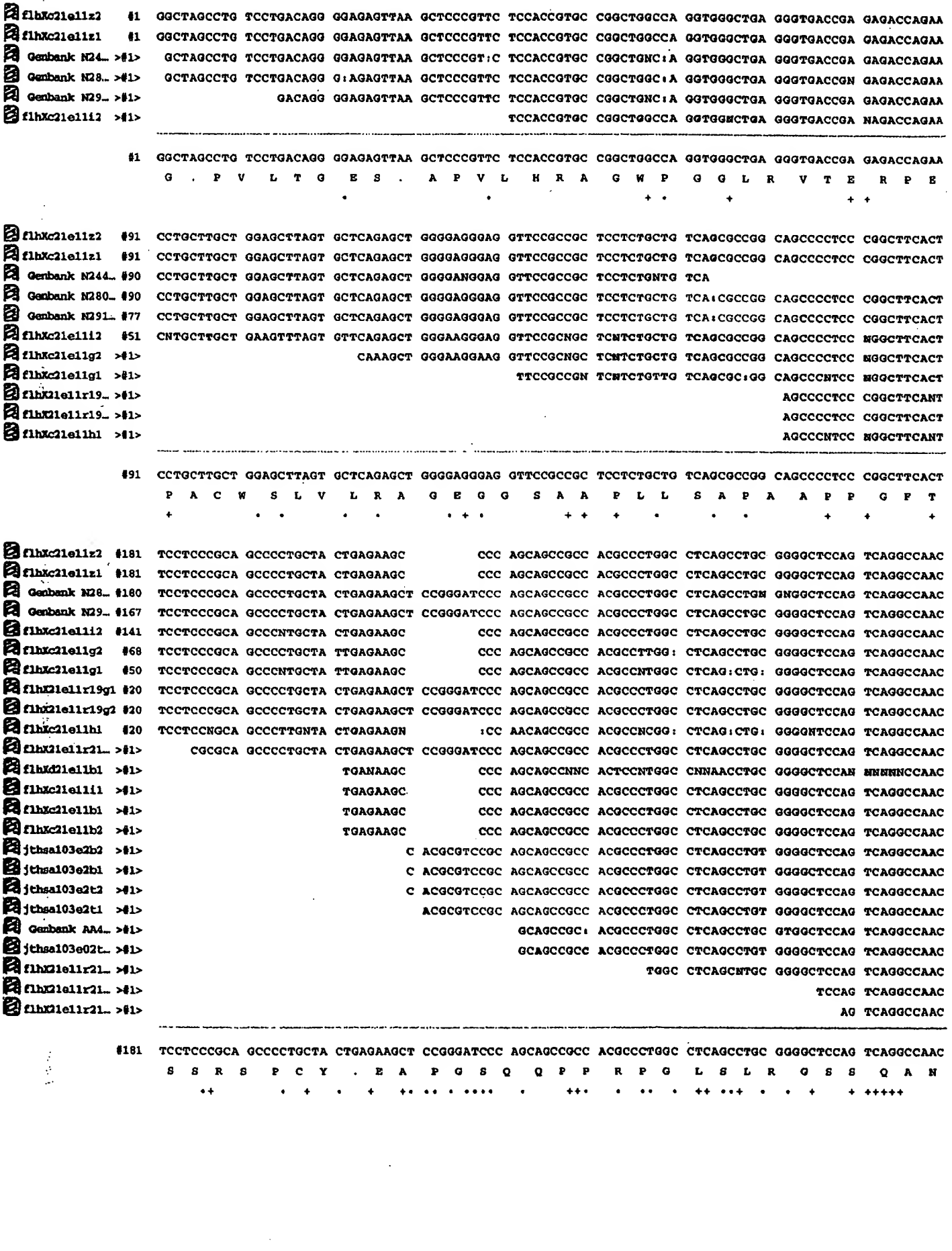
Sequencher™ "21e11racefinal"



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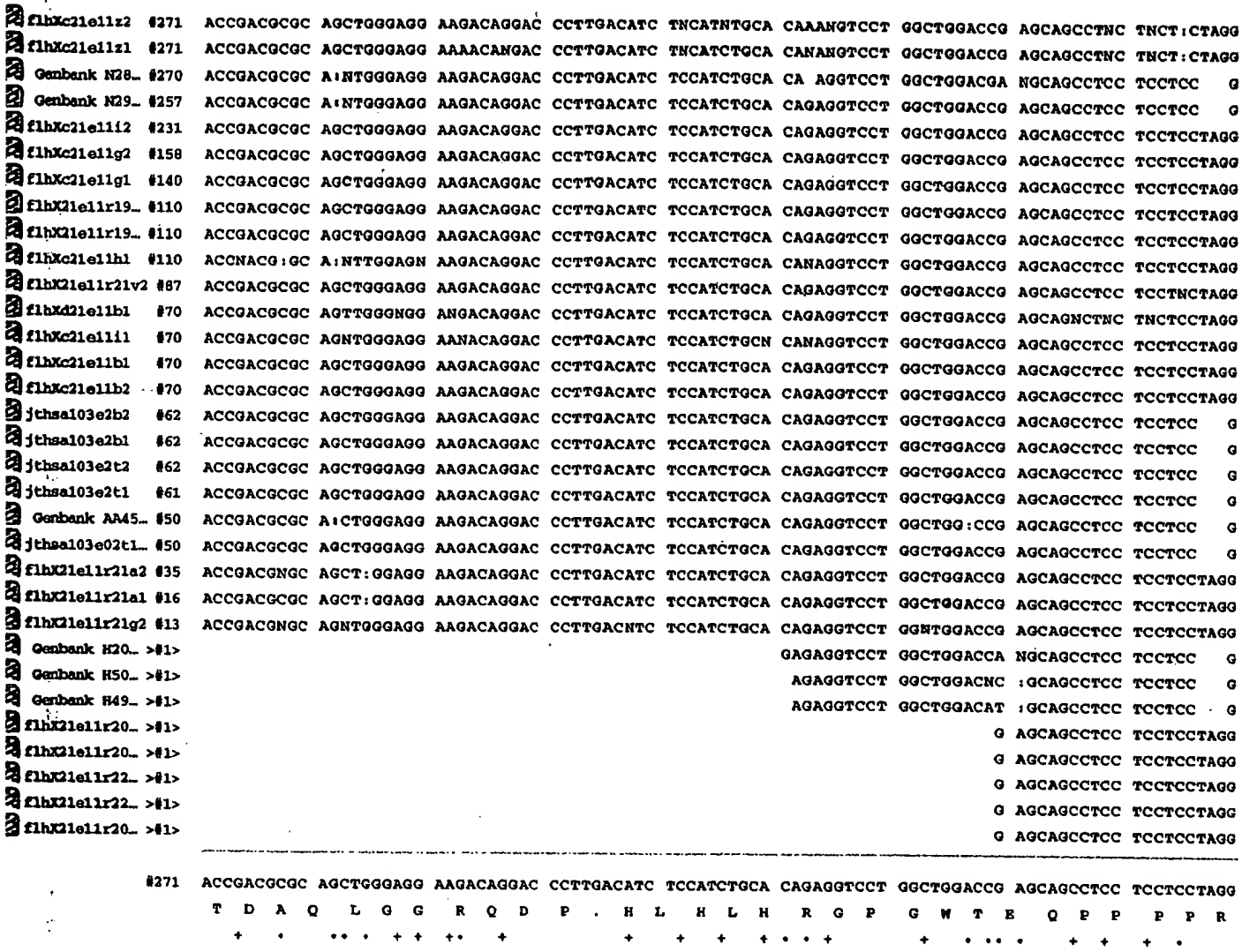

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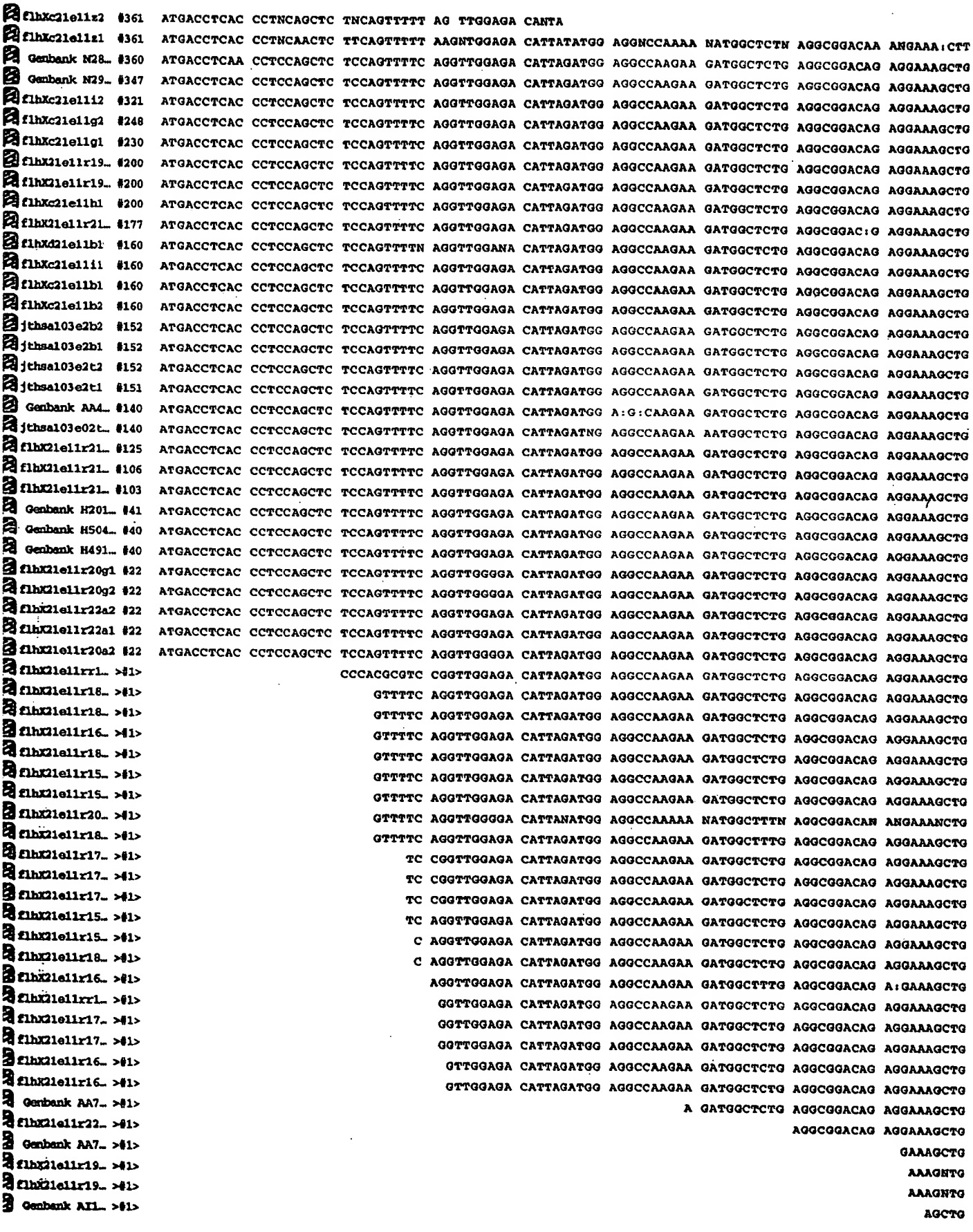

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Sequencher™ "21e11racefinal"

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Sequencher™ "21e11racefinal"

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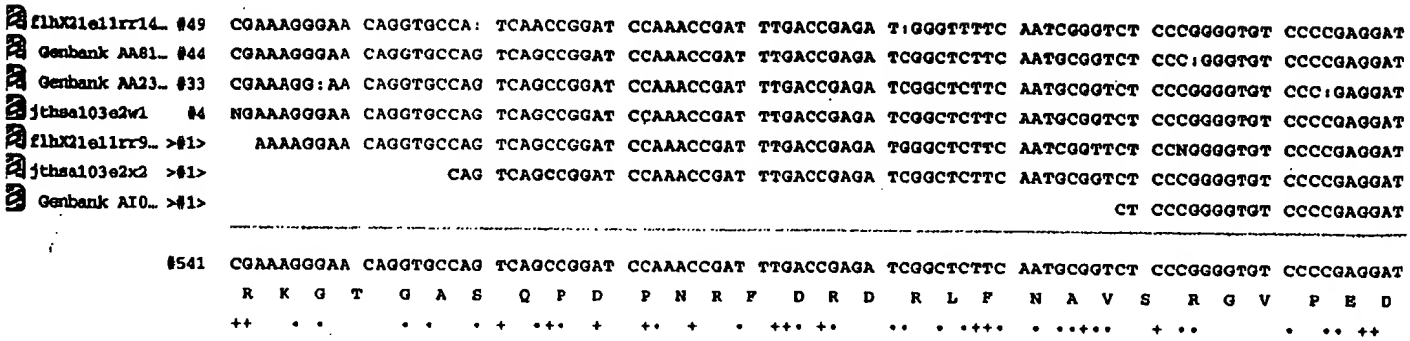
21e11a

Sequencher™ "21e11racefinal"



21e11a

Sequencher™ "21e11racefinal"

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flhXc21e11h1  #470  CTGGCTGGAC TTCCAGAGTA CCTGAGCAAG ACCAGCAAGT ACCTCACCGA CTCGGAATAC ACAGAGGGCT CCACAGGTAA GACGTGCCTG
flhXc21e11b1  #430  CTGNTTGGAC TT
flhXc21e11b2  #430  CTGGCTGGAC TTTCAGAGTA CCTGAGCCAG ACCAGCAAGT ACCTC:CCGA CTCGGAATAC ACAGAAGGCT TCACAAGTAA AACGTGCCTG
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jthsa103e2t1  #421  CTGGCTGGAC TTCCAGAGTA CCTGAGCAAG ACCAGCAAGT ACCTCACCGA CTCGGAATAC ACAGANGGCT NCACANGTAA GACGTGCCTG
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Genbank AI1_  #186  CTGGCTGGAC TTCCAGAGTA CCTGAGCAAG ACCAGCAAGT ACCTCACCGA CTCGGAATAC ACAGAGGGCT CCACAGGTAA GACGTGCCTG
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flhX21e11r17_ #153  CTGGCTGGAC TTCCAGAGTA CCTGAGCAAG ACCAGCAAGT ACCTCACCGA CTCGGAATAC ACAGA
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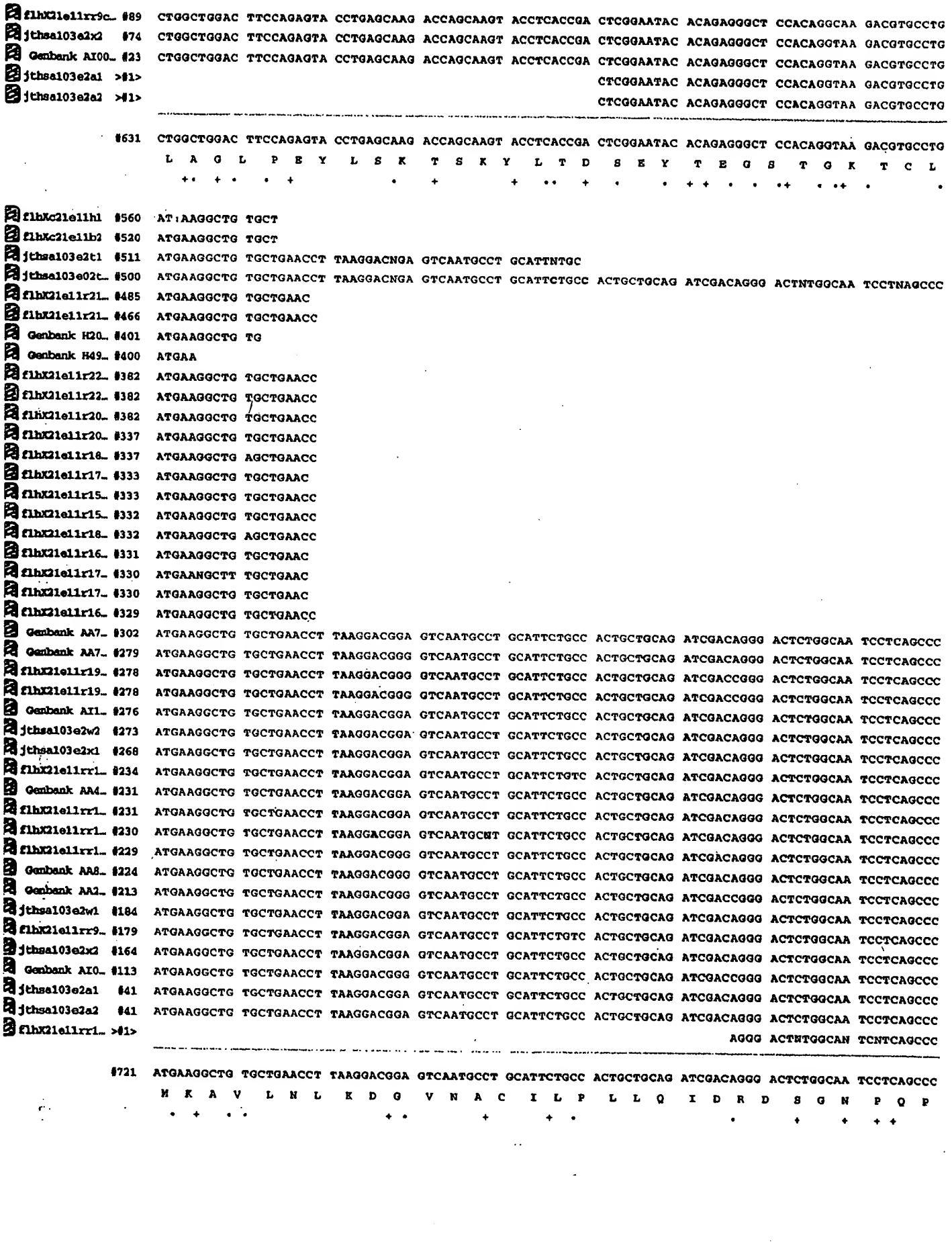
21e11a

Sequencher™ "21e11racefinal"



21e11a

Sequencer™ "21e11racefinal"

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Genbank AI1... #366  CTGGTAAATG CCCAGTGCAC AGATGACTAT TACCGAGGCC ACAGCGCTCT GCACATCGCC ATTGAGAAGA GGAGTCTGCA GTGTGTGAAG
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jthsa103e2x1  #358  CTGGTAAATG CCCAGTGCAC AGATGACTAT TACCGAGGCC ACAGCGCTCT GCACATCGCC ATTGAGAAGA GGAGTCTGCA GTGTGTGAAG
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Sequencher™ "21e11racefinal"

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jthsa103e2w2  #453  CTCCTGGTGG AGAATGGGGC CAATGTGCAT GCCCGGGCCT GCGGCCGCT
jthsa103e2x1  #448  CTCCTGGTGG AGAATGGGGC CAATGTGCAT GCCCGGGCCT GCGGCCGCT
flhX21e11rr1… #414  CTCCTGGTGG AGAATGGGGC CAATGTGCAT GCCCGGGCCT GCGACCGCTT CTTCCAGAAG GGCCAAGGGA CTTGCTTTTA TTTCGGTGAG
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flhX21e11rr1… #410  CTCCTGGTGG AGAATGGGGC CAATGTGCAT GCCCGGGCCT GCGGCCGCTT CTTCCAGAAG GGCCAAGGGA CTTGCTTTTA TTTCGGTGAG
flhX21e11rr1… #409  CTCCTGGTGG AGAATGGGGC CAATGTGCAT GCCCGGGCCT GCGGCCGCTT CTTCCAGAAG GGCCAAGGGA CTTGCTTTTA TTTCGGTGAG
 Genbank AA2… #393  CTCCTGGTGG AGAATGGGGC CAATGTGCAT GCCCGGGCCT G
jthsa103e2w1  #364  CTCCTGGTGG AGAATGGGGC CAATGTGNAT GCCCGGGCCT GCGGCCGCT
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jthsa103e2x2  #344  CTCCTGGTGG AGAATGGGGC CAATGTGCAT GCCCGGGCCT GCGGCCGCT
jthsa103e2a1  #221  CTCCTGGTGG AGAATGGGGC CAATGTGCAT GCCCGGGCCT GCGGCCGCT
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flhX21e11rha2 >#1>                                           CGGCCGCTT CTTCCAGAAG GGCCAAGGGA CTTGCTTTTA TTTCGGTGAG
flhX21e11rmv2 >#1>                                             GCCGCTT CTTCCAGAAG GGCCAAGGGA CTTGCTTTTA TTTCGGTGAG
flhX21e11r1v1 >#1>                                             CCGCTT CTTCCAGAAG GGCCAAGGGA CTTGCTTTTA TTTCGGTGAG
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 Genbank AA9… >#1>                                                                                  TCGGTGAG
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                              +           •     +           •    +           +  •+
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21e11a

Sequencher™ "21e11racefinal"

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flhX21e11rr1... #500   CTACCCCTCT CNTTGGCCGC TTGCACCAAG CAGTGGGATG TGGTAAGCTA CCTCCTGGAG AACCCACACC AGCCCGCCAG CCTGCAGGCC
flhX21e11rr1... #499   CTACCCCTCT CTTTGGCCGC TTGCACCAAG CAGTGGGATG TGGTAAGCTA CCTCCTGGAG AACCCACACC GGCCCGCCAG CCTGCAGGCC
flhX21e11rr9... #449   CTACCCCTCT CTTTGGCCGC TTGCACCAAG CAGTGGGATG TGGTAAGCTA CCTCCTGGAG AACCCACACC AGCCCGCCAG CCTGCAGGCC
flhX21e11rr1... #205   CTACCCCTCT CTTTGNCCGC TTGCACCAAG CAGTGGGATG TGGTAAGCTA CCTCCTGGAG AACCCACACC GGCCCGCCAG CCTGCAGGCC
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frhob012c04s1... #51   CTACCCCTCT CTTTGGCCGC TTGCACCAAG CAGTGGGATG TGGTAAGCTA CCTCCTGGAG AACCCACACC AGCCCGCCAG CCTGCAGGCC
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flhX21e11rlv1  #47   CTACCCCTCT CTTTGGCCGC TTGCACCAAG CAGTGGGATG TGGTAAGCTA CCTCCTGGAG AACCCACACC AGCCCGCCAG CCTGCAGGCC
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Genbank AA992... #9   CTACCCCTCT CTTTGGCCGC TTGCACCAAG CAGTGGGATG TGGTAAGCTA CCTCCTGGAG AACCCACACC AGCCCGCCAG CCTGCAGGCC
Genbank AA995... #9   CTACCCCTCT CTTTGGCCGC TTGCACCAAG CAGTGGGATG TGGTAAGCTA CCTCCTGGAG AACCCACACC AGCCCGCCAG CCTGCAGGCC
flhX21e11rr9... >#1>      CCCCTCT CTTTGGCCGC TTGCACCAAG CAGTGGGATG TGGTAAGCTA CCTCCTGGAG AACCCACACC AGCCCGCCAG CCTGCAGGCC
flhX21e11rr9... >#1>      CCCCTCT CTTTGGCCGC TTGCACCAAG CAGTGGGATG TGGTAAGCTA CCTCCTGGAG AACCCACACC AGCCCGCCAG CCTGCAGGCC
jthKb051a01t... >#1>            CTTTGGCCGC TTGCNCCAAG CAGNGGGATG TGGTAAGCTA CCTNCTGGAG AACCCACACC AGNCCGCCAG CCTGCAGGCC
flhX21e11rr1... >#1>                                                        TA CCTCCTGGAG AACCCACACC AGCCCGCCAG CCTGCAGGCC
flhX21e11rr1... >#1>                                                        TA CCTCCTGGAG AACCCACACC AGCCCGCCAG CCTGCAGGCC
```

```
#991   CTACCCCTCT CTTTGGCCGC TTGCACCAAG CAGTGGGATG TGGTAAGCTA CCTCCTGGAG AACCCACACC AGCCCGCCAG CCTGCAGGCC
        L  P  L  S   L  A  A   C  T  K   Q  W  D  V   V  S  Y   L  L  E   N  P  H  Q   P  A  S   L  Q  A
        +           +  ++        +        +  +                 +  .          +   .  +  +
```

```
flhX21e11rr1... #594   ACTGACTCCC AGGGCAACAC AGTC
flhX21e11rr1... #591   ACTGACTCCC AGGGCAACAC NGT
flhX21e11rr1... #590   ACTGACTCCC AGGGCAACAC AGT
flhX21e11rr1... #589   ACTGACTCCC AGGGCAACAC AGTCC
flhX21e11rr9... #539   ACTGACTCCC AGGGCAACAC AGTC
flhX21e11rr1... #295   ACTGACTCCC AGGGCAACAC AGTC
frhob12c4g1... #141   ANTGACTCCC AGGGCAACAC AGTCCTGCAT GCCCTAGTGA TGATGTCGGN CAANTCAGCT GAGAACATTG CACTGGTGAC CAGCATGTAT
frhob012c04s... #141   ACTGACTCCC AGGGCAACAC AGTCCTGCAT GCCCTAGTGA TGATCTCGGA CAACTCAGCT GAGAACATTG CACTGGTGAC CAGCATGTAT
frhob012c04s... #141   ACTGACTCCC AGGGCAACAC AGTCCTGCAT GCCCTAGTGA TGATCTCGGA CAACTCAGCT GAGAACATTG CACTGGTGAC CAGCATGTAT
flhX21e11rha2 #140   ACTGACTCCC AGGGCAACAC AGTCCTGCAT GCCCTAGTGA TGATCTCGGA CAACTCAGCT GAGAACA
flhX21e11rmv2 #138   ACTGACTCCC AGGGCAACAC AGTCCTGCAT GCCCTAGTGA TGATCTCGGA CAACTCAGCT GAGAACA
flhX21e11rlv1 #137   ACTGACTCCC AGGGCAACAC AGTCCTGCAT GCCCTAGTGA TGATCTCGGA CAACTCAGCT GAGAACA
frhoc12c4h3... #133   ACTGACTCCC AGGGCAACAC AGTCCTGCAT GCCCTAGTGA TGATCTCGGA CAACTCAGCT GAGAACATTG CACTGGTGAC CAGCATGTAT
flhX21e11rlv2 #130   ACTGACTCCC AGGGCAACAC AGTCCTGCAT GCCCTAGTGA TGATCTCGGA CAACTCAGCT GAGAACA
flhX21e11rmv1 #126   ACTGACTCCC AGGGCAACAC AGTCCTGCAT GCCCTAGTGA TGATGTCGGA CAACTCAGCT GAGAAC
flhX21e11rja2 #116   ACTGACTCCC AGGGCAACAC AGTCCTGCAT GCCCTAGTGA TGATCTCGGA CAACTCAGCT GAGAACA
Genbank AA99... #99   ACTGACTCCC AGGGCAACAC AGTCCTGCAT GCCCTAGTGA TGATCTCGGA CAACTCAGCT GAGAACATTG CACTGGTGAC CAGCATGTAT
Genbank AA99... #99   ACTGACTCCC AGGGCAACAC AGTCCTGCAT GCCCTAGTGA TGATCTCGGA CAACTCAGCT GAGAACATTG CACTGGTGAC CAGCATGTAT
flhX21e11rr9a1 #88   ACTGACTCCC AGGGCAACAC AGTCCTGCAT GCCCTAGTGA TGATCTCGGA CAACTCAGCT GAGAACA
flhX21e11rr9a2 #88   ACTGACTCCC AGGGCAACAC AGTCCTGCAT GCCCTAGTGA TGATCTCGGA CAACTCAGCT GAGAACA
jthKb051a01t1... #81   ACTGACTCCC AGGGCAACAC AGTCCTGCAT GCCCTAGTGA TGATCTCGGA CAACTCAGCT GAGAA
flhX21e11rr11... #43   ACTGACTCCC AGGGCAACAC AGTC
flhX21e11rr11... #43   ACTGACTCCC AGGGCAACAC AGTN
```

```
#1081  ACTGACTCCC AGGGCAACAC AGTCCTGCAT GCCCTAGTGA TGATCTCGGA CAACTCAGCT GAGAACATTG CACTGGTGAC CAGCATGTAT
        T  D  S  Q   G  N  T   V  L  H   A  L  V  M   I  S  D   N  S  A   E  N  I  A   L  V  T   S  M  Y
        +              +  +                 .   +   +
```

21e11a

Sequencher™ "21e11racefinal"

```
frhob12c4g1.... #231  GATGGGCTCC TCCAAGCTGG GGCCCGCCTC TGCCCTACCG TGCAGCTTGA GGACATCCGC AACCTNCAGG ATCTCACGCC TCTGAAGCTG
frhob012c04s... #231  GATGGGCTCC TCCAAGCTGG GGCCCGCCTC TGCCCTACCG TGCAGCTTGA GGACATCCGC AACCTGCAGG ATCTCACGCC TCTGAAGCTG
frhob012c04s... #231  GATGGGCTCC TCCAAGCTGG GGCCCGCCTC TGCCCTACCG TGCAGCTTGA GGACATCCGC AACCTGCAGG ATCTCACGCC TCTGAAGCTG
frhoc12c4h3.... #223  GATGGGCTCC TCCAAGCTGG GGCCCGCCTC TGCCCTACCG TGCAGCTTGA GGACATCCGC AACCTGCAGG ATCTCACGCC TCTGAAGCTG
Genbank AA9... #189  GATGGGCTCC TCCAAGCTGG GGCCCGCCTC TGCCCTACCG TGCAGCTTGA GGACATCCGC AACCTGCAGG ATCTCACQ
Genbank AA9... #189  GATGGGCTCC TCCAAGCTGG GGCCCGCCTC TGCCCTACCG TGCAGCTTGA GGACATCCGC AACCTGCAGG ATCTCACGCC TCTGAAGCTG
jthLa029c10t... >#1>                        CGCCTC TGCCCTACCG TGCAGCTTGA GGACATCCGC AACCTGCAGG ATCTCACGCC TCTGAAGCTG
Genbank W38... >#1>                           CCTC TGCCCTACCG TGCAGCTTGA GGACATCCGC AACCTGCAGG ATCTCACGCC TCTGAAANTG
                     ---------------------------------------------------------------------------------------------------

                #1171  GATGGGCTCC TCCAAGCTGG GGCCCGCCTC TGCCCTACCG TGCAGCTTGA GGACATCCGC AACCTGCAGG ATCTCACGCC TCTGAAGCTG
                        D  G  L  L  Q  A  G  A  R  L  C  P  T  V  Q  L  E  D  I  R  N  L  Q  D  L  T  P  L  K  L
                                                                                    +                    .+


frhob12c4g1.... #321  GCCGCCAAGG AGGGCAAGNT CGANATTTTC AGGCACATCC TGCA
frhob012c04s... #321  GCCGCCAAGG AGGGCAAGAT CGAGATTTTC AGGCACATCC TGCAGCGGGA GTTTTCAGGA CTGAGCCACC TTTCCCGAAA GTTCACCGAG
frhob012c04s... #321  GCCGCCAAGG AGGGCAAGAT CGAGATTTTC AGGCACATCC TGCAGCGGGA GTTTTCAGGA CTGAGCCACC TTTCCCGAAA GTTCACCGAG
frhoc12c4h3.... #313  GCCGCCAAGG AGGGCAAGAT CGAGATTTTC AGGCACATCC TGCAGCGGGA GTTTTCAGGA CTGAGCCACC TTTCCCGAAA GTTCACCGAG
Genbank AA9... #279  GCCGCCAAGG AGGGCAAGAT CGAGATCTTC AGGCACATCC T
jthLa029c10t1... #67  GCCGCCAAGG AGGGCAAGAT CGAGATTTTC AGGCACATCC TGCAGCGGGA GTTTTCAGGA CTGAGCCACC TTTCCCGAAA GTTCACCGAG
Genbank W386... #65  GCCGCCAAGG AGGGCAAGAT CGAGATTTTC AGGCACATCC TGCAGCGGGA GTTNTCAGGA CTGAGCCACC TTTCCCGAAA GTTCACCGAG
Genbank AA3... >#1>                                                                TTCAGGA CTGAGCCACC TTTCCCGAAA GTTCACCGAG
                     ---------------------------------------------------------------------------------------------------

                #1261  GCCGCCAAGG AGGGCAAGAT CGAGATTTTC AGGCACATCC TGCAGCGGGA GTTTTCAGGA CTGAGCCACC TTTCCCGAAA GTTCACCGAG
                        A  A  K  E  G  K  I  E  I  F  R  H  I  L  Q  R  E  F  S  G  L  S  H  L  S  R  K  F  T  E
                                       +     +  .                          +


frhob012c04s... #411  TGGTGCTATG GGCCTGTCCG GGTGTCGCTG TATGACCTGG CTTCTGTGGA CAGCTGTGAG GAGAACTCAG TGCTGGAGAT CATTGCCTTT
frhob012c04s... #411  TGGTGCTATG GGCCTGTCCG GGTGTCGCTG TATGACCT:G CTTCTGTGGA CAGCTGTGAG GAGAACTCAA TGCTGGAGAT CATTGCCTTT
frhoc12c4h3.... #403  TGGTGCTATG GGCCTGTCCG GGTGTCGCTG TATGACCTGG CTTCTGTGGA CAGCTGTGAG GAGAACTCAG TGCTGGAGAT CATTGCCTTT
jthLa029c10t... #157  TGGTGCTATG GGCCTGTCCG GGTGTCGCTG TATGACCTGG CTTCTGTGGA CAGCTGTGAG GAGAACTCAG TGCTGGAGAT CATTGCCTTT
Genbank W38... #155  TGGTGCTATG GGCCTGTCCG GGTGTCGCTG TATGACCTGG CTTCTGTGGA CAGCTGTGAG GAGAACTCAG TGCTGGAGAT CATTGCCTTT
Genbank AA35... #38  TGGTGCTATG GGCCTGTCCG GGTGTCGCTG TATGACCTGG CTTCTNTGGA CAGCTGTNAG GAGAACTCAG TGCTGGAGAT CATTGCCTTT
frhob12c4c1.... >#1>            GGCCTGTNCG GGTGTCNCTG TATGACNTGG CTTCTGTGNA CAGCTGTGAN GAGAACTCAG TGCTGGAGAT CATTGCCTTT
Genbank N24... >#1>                                                                GAGAACTCAG TGCTGGAGAT CATTGNCTTT
                     ---------------------------------------------------------------------------------------------------

                #1351  TGGTGCTATG GGCCTGTCCG GGTGTCGCTG TATGACCTGG CTTCTGTGGA CAGCTGTGAG GAGAACTCAG TGCTGGAGAT CATTGCCTTT
                        W  C  Y  G  P  V  R  V  S  L  Y  D  L  A  S  V  D  S  C  E  E  N  S  V  L  E  I  I  A  F
                                    +        +        + .      + +       + +        .              +


frhob012c04s... #501  CATTGCAAGA GCCCGCACCG ACACCGAATG GTCGNTTTGG AGCCCCTGAA CAAACTGCTG C
frhob012c04s... #501  CATTGCAAGA ACCCGCACCG ACACCGAATG GTCGNTTTGG AGCCCCTGAA CAAACTGCTG CANGCGAAAT GGGATCTGCT CAT:CCCAAG
frhoc12c4h3.... #493  CATTGCAAGA GCCCGCACCG ACACCGAATG GTCGTTTTGN AGCCCCTGAA CAAACTGCTG CAGGCGAAAT GGGATCTGCT CATCCCCAA
jthLa029c10t... #247  CATTGCAAGA GCCCGNACCG ACACCGAATG GTCGTTTTGG AGCCCCTGAA CAAACTGCTG CANGCGAAAT GGGATCTGCT CATNCNCAAG
Genbank W38... #245  CATTGCAAGA GCCCGCACCG ACACCGAATG GTCGTTTTGG AGCCCCTGAA CAAACTGCTG CAGGCGAAAT GGGATCTGCT CATCCCCAAG
Genbank AA3... #128  CATTGCAAGA GCCCGCACCG ACACCGAATG GTCGTTTTGG AGCCCCTGAA CAAACTGCTG CAGGCGAAAT GGGATCTGCT CATCCCCAAG
frhob12c4c1.a... #81  CATTGCAAGA GNCCGCACCG ACACNGAATG GTCGTTTTGG AGCCCCTGAA CAAACTGCTG CAGNCGAAAT GGGATCTGCT CATCCCCAAG
Genbank N242... #31  CATTGCAAGA GCCCGNACCG ACACCGAATG GTCGTTTTGG AGCCCCTGAA CAAACTGCTG CAGGCGAAAT GGGATCTGCT CATCCCCAAG
                     ---------------------------------------------------------------------------------------------------

                #1441  CATTGCAAGA GCCCGCACCG ACACCGAATG GTCGTTTTGG AGCCCCTGAA CAAACTGCTG CAGGCGAAAT GGGATCTGCT CATCCCCAAG
                        H  C  K  S  P  H  R  H  R  M  V  V  L  E  P  L  N  K  L  L  Q  A  K  W  D  L  L  I  P  K
                                 .+  +        +        +    +                          ++                 . +
```

21e11a

Sequencher™ "21e11racefinal"

```
Achrb21e11 … #425  GGCACTAAGC CAGATGGCAG CCCGGATGAG CGCTGGTGCT TCAGGGTGGA GGAGGTGAAC TGGGCTTCAT GGGAGCAGAC GCTGCCTACG
frhob12c4d1.… >#1>                                                                  TCAT GGGAGCAGAC GCTGCCTACG
                   ---------- ---------- ---------- ---------- ---------- ---------- ---------- ----------

#2431              GGCACTAAGC CAGATGGCAG CCCGGATGAG CGCTGGTGCT TCAGGGTGGA GGAGGTGAAC TGGGCTTCAT GGGAGCAGAC GCTGCCTACG
                    G  T  K  P  D  G  S  P  D  E  R  W  C  F  R  V  E  E  V  N  W  A  S  W  E  Q  T  L  P  T


Achrb21e11 … #515  CTGTGTGAGG ACCCGTCAGG GGCAGGTGTC CCTCGAACTC TCGAGAACCC TGTCCTGGCT TCCCCTCCCA AGGAGGATGA GGATGGTGCC
frhob12c4d1.a… #25  CTGTGTGAGG ACCCGTCAGG GGCAGGTGTC CCTCGAACTC TCGAGNACCC TGTCCTGGCT TCCCCTCCCA AGGAGGATGA GGATGGTGCC
                   ---------- ---------- ---------- ---------- ---------- ---------- ---------- ----------

#2521              CTGTGTGAGG ACCCGTCAGG GGCAGGTGTC CCTCGAACTC TCGAGAACCC TGTCCTGGCT TCCCCTCCCA AGGAGGATGA GGATGGTGCC
                    L  C  E  D  P  S  G  A  G  V  P  R  T  L  E  N  P  V  L  A  S  P  P  K  E  D  E  D  G  A
                                                                                 +


Achrb21e11 … #605  TCTGAGGAAA ACTATGTGCC CGTCCAGCTC CTCCAGTCCA ACTGATGGCC CAGATGCAGC AGGAGGCCAG AGGACAGAGC AGAGGATCTT
frhob12c4d1.… #115  TCTGAGGAAA ACTATGTGCC CGTCCAGCTC CTCCAGTCCA ACTGATGGCC CAGATGCAGC AGGAGGCCAG AGGACAGAGC ANAGGATCTT
                   ---------- ---------- ---------- ---------- ---------- ---------- ---------- ----------

#2611              TCTGAGGAAA ACTATGTGCC CGTCCAGCTC CTCCAGTCCA ACTGATGGCC CAGATGCAGC AGGAGGCCAG AGGACAGAGC AGAGGATCTT
                    S  E  E  N  Y  V  P  V  Q  L  L  Q  S  N  .  W  P  R  C  S  R  R  P  E  D  R  A  E  D  L
                                                                                                       +


Achrb21e11 … #695  TCCAACCACA TCTGCTGGCT CTGGGGTCCC AGTGAATTCT GGTGGCAAAT ATATATTTTC ACTAACTCAA AAAAAAAAAA AAAAA
frhob12c4d1.… #205  TCCAACCACA TCTGCTGGCT CTGGGGTCCC AGTGAATTCT GGTGGCAAAT ATATATTTTC ACTAACTCAA AAAAAAAAAA AAAAAAAAAA
                   ---------- ---------- ---------- ---------- ---------- ---------- ---------- ----------

#2701              TCCAACCACA TCTGCTGGCT CTGGGGTCCC AGTGAATTCT GGTGGCAAAT ATATATTTTC ACTAACTCAA AAAAAAAAAA AAAAAAAAAA
                    S  N  H  I  C  W  L  W  G  P  S  E  F  W  W  Q  I  Y  I  F  T  N  S  K  K  K  K  K  K  K


frhob12c4d1.… #295  AAAAAAAAAA AAAAAAAAA
                   ---------- ---------

#2791              AAAAAAAAAA AAAAAAAAA
                    K  K  K  K  K  K
```

Exhibit C

BLASTP vs. PNU (AA) flh21e11orfaa - 5:26:57 pm on Dec 21 98

BLASTP 1.4.10MP-WashU [30-Aug-96] [Build 20:24:58 Oct 21 1996]

Reference: Altschul, Stephen F., Warren Gish, Webb Miller, Eugene W. Myers, and David J. Lipman (1990). Basic local alignment search tool. J. Mol. Biol. 215:403-10.

Query= flh21e11orfaa
(764 letters)

Database: /disk0/asap/databases/db/NRP/protxnu
345,099 sequences; 106,000,184 total letters.
Searching.....done

Sequences producing High-scoring Segment Pairs:	High Score	Smallest Sum Probability P(N)	N
GP:gi|2570933 (AF029310) vanilloid receptor subtype 1 [Ra...	336	1.9e-221	7
GPU:gi|3986159|gnl|PID|d1035925 (AB015231) VR1sk [Mus mus...	299	9.8e-136	6
GP:gi|2911863 (AF047660) contains similarity to ankyrin r...	103	6.5e-20	8
GP:gi|3875319|gnl|PID|e1344970 (Z74030) similar to ankyri...	97	1.1e-19	7
GP:gi|2642590 (AF031408) olfactory channel [Caenorhabditi...	93	3.6e-16	6
GP:gi|2854148 (AF045639) contains similarity to ankyrin r...	93	4.1e-16	6
GP:gi|3879753|gnl|PID|e1349345 (Z72514) Similarity to Hum...	73	3.6e-11	6
GP:gi|3287188|gnl|PID|e315126 (Y10601) ankyrin-like prote...	71	2.7e-08	6
SP:SP:sp|P48994|TRPL_DROME TRANSIENT-RECEPTOR-POTENTIAL L...	69	2.2e-05	4
GP:gi|1841966 (U65916) ankyrin [Rattus norvegicus]	72	5.6e-05	3

WARNING: Descriptions of 4 database sequences were not reported due to the limiting value of parameter V = 10.

>GP:gi|2570933 (AF029310) vanilloid receptor subtype 1 [Rattus norvegicus]
Length = 838

Score = 336 (156.0 bits), Expect = 1.9e-221, Sum P(7) = 1.9e-221
Identities = 67/112 (59%), Positives = 84/112 (75%)

```
Query:   206 FYFGELPLSLAACTKQWDVVSYLLENPHQPASLQATDSQGNTVLHALVMISDNSAENIAL 265
             FYFGELPLSLAACT Q  +V +LL+N  QPA + A DS GNTVLHALV ++DN+ +N
Sbjct:   245 FYFGELPLSLAACTNQLAIVKFLLQNSWQPADISARDSVGNTVLHALVEVADNTVDNTKF 304

Query:   266 VTSMYDGLLQAGARLCPTVQLEDIRNLQDLTPLKLAAKEGKIEIFRHILQRE 317
             VTSMY+ +L  GA+L PT++LE+I N + LTPL LAA  GKI +  +ILQRE
Sbjct:   305 VTSMYNEILILGAKLHPTLKLEEITNRKGLTPLALAAASSGKIGVLAYILQRE 356
```

Score = 316 (146.7 bits), Expect = 1.9e-221, Sum P(7) = 1.9e-221
Identities = 65/138 (47%), Positives = 93/138 (67%)

```
Query:    66 ASQPDPNRFDRDRLFNAVSRGVPEDLAGLPEYLSKTSKYLTDSEYTEGSTGKTCLMKAVL 125
             A +  P  +DR  +F+AV++   ++L  L  +L ++ K LTDSE+ +  TGKTCL+KA+L
Sbjct:   104 AGEKPPRLYDRRSIFDAVAQSNCQELESLLPFLQRSKKRLTDSEFKDPETGKTCLLKAML 163

Query:   126 NLKDGVNACILPLLQIDRDSGNPQPLVNAQCTDDYYRGHSALHIAIEKRSLQCVKLLVEN 185
             NL +G N  I  LL + R + + +  VNA  TD YY+G +ALHIAIE+R++  V LLVEN
Sbjct:   164 NLHNGQNDTIALLLDVARKTDSLKQFVNASYTDSYYKGQTALHIAIERRNMTLVTLLVEN 223

Query:   186 GANVHARACGRFFQKGQG 203
```

```
            GA+V A A G FF+K +G
Sbjct:   224 GADVQAAAANGDFFKKTKG 241

 Score = 299 (138.8 bits), Expect = 1.9e-221, Sum P(7) = 1.9e-221
 Identities = 69/175 (39%), Positives = 94/175 (53%)

Query:   391 FFLNFLCNLIYMFIFTAVAYHQPTLKKAAPHLKAEVGNSMLLTGHILILLGGIYLLVGQL 450
            F+ NF    +YM IFTA AY++P        LK  VG+   +TG IL +          +
Sbjct:   434 FYFNFFVYCLYMIIFTAAAYYRPVEGLPPYKLKNTVGDYFRVTGEILSVXXXXXXXXRGI 493

Query:   451 WYFWRRHVFIWISFIDSYFEILFLFQALLKPVSQVLCFLAIEWYLPLLVSALVLGWLNLL 510
             YF +R   +   F+DSY EILF  Q+L   VS VL F   + Y+  +V +L +GW N+L
Sbjct:   494 QYFLQRRPSLKSLFVDSYSEILFFVQSLFLVSVVLYFSQRKEYVASMVFSLAMGWTNML 553

Query:   511 YYTRGFQHTGIYSVMIQKVILRDLLRFLLIYLVFLFGFAVALVSLSQEAWRPEAP 565
            YYTRGFQ  GIY+VMI+K+ILRDL R               A+V+L ++      P
Sbjct:   554 YYTRGFQQMGIYAVMIEKMILRDLCRXXXXXXXXXXXXXTAVVTLIEDGKNNSLP 608

 Score = 281 (130.5 bits), Expect = 1.9e-221, Sum P(7) = 1.9e-221
 Identities = 54/95 (56%), Positives = 70/95 (73%)

Query:   586 GAQYRGILEASLELFKFTIGMGELAFQEQLHFRGMVLLLLLAYVLLTYILLLNMLIALMS 645
            G  Y  +    LELFKFTIGMG+L F E   F+ + ++LLLAYV+LTYILLLNMLIALM
Sbjct:   624 GNSYNSLYSTCLELFKFTIGMGDLEFTENYDFKAVFIILLLAYVILTYILLLNMLIALMG 683

Query:   646 ETVNSVATDSWSIWKLQKAISVLEMENGYWWCRKK 680
            ETVN +A +S +IWKLQ+AI++L+ E  +  C +K
Sbjct:   684 ETVNKIAQESKNIWKLQRAITILDTEKSFLKCMRK 718

 Score = 162 (75.2 bits), Expect = 1.9e-221, Sum P(7) = 1.9e-221
 Identities = 28/38 (73%), Positives = 34/38 (89%)

Query:   323 HLSRKFTEWCYGPVRVSLYDLASVDSCEENSVLEIIAF 360
            HLSRKFTEW YGPV  SLYDL+ +D+CE+NSVLE+IA+
Sbjct:   364 HLSRKFTEWAYGPVHSSLYDLSCIDTCEKNSVLEVIAY 401

 Score = 144 (66.9 bits), Expect = 1.9e-221, Sum P(7) = 1.9e-221
 Identities = 25/47 (53%), Positives = 31/47 (65%)

Query:   678 RKKQRAGVMLTVGTKPDGSPDERWCFRVEEVNWASWEQTLPTLCEDP 724
            RK  R+G +L VG  PDG  D RWCFRV+EVNW +W   +  + EDP
Sbjct:   717 RKAFRSGKLLQVGFTPDGKDDYRWCFRVDEVNWTTWNTNVGIINEDP 763

 Score = 94 (43.6 bits), Expect = 1.9e-221, Sum P(7) = 1.9e-221
 Identities = 15/30 (50%), Positives = 24/30 (80%)

Query:   363 KSPHRHRMVVLEPLNKLLQAKWDLLIPKFF 392
            ++P+RH M+++EPLN+LLQ KWD  + + F
Sbjct:   405 ETPNRHDMLLVEPLNRLLQDKWDRFVKRIF 434

 Score = 46 (21.4 bits), Expect = 1.3e-162, Sum P(6) = 1.3e-162
 Identities = 11/48 (22%), Positives = 24/48 (50%)

Query:   435 HILILLGGIYLLVGQLWYFWRRHVFIWISFIDSYFEILFLFQALLKPV 482
            H ++L+  +  L+   W  + + +F +  F+   + I+F   A  +PV
Sbjct:   410 HDMLLVEPLNRLLQDKWDRFVKRIFYFNFFVYCLYMIIFTAAAYYRPV 457

 Score = 37 (17.2 bits), Expect = 2.4e-169, Sum P(7) = 2.4e-169
 Identities = 8/22 (36%), Positives = 13/22 (59%)

Query:   297 PLKLAAKEGKIEIFRHILQREF 318
            PL LAA   ++ I + +LQ  +
Sbjct:   251 PLSLAACTNQLAIVKFLLQNSW 272
```

```
 Score = 37 (17.2 bits), Expect = 1.9e-111, Sum P(7) = 1.9e-111
 Identities = 8/26 (30%), Positives = 15/26 (57%)

Query:   206 FYFGELPLSLAACTKQWDVVSYLLEN 231
             +Y G+  L +A    +   +V+ L+EN
Sbjct:   198 YYKGQTALHIAIERRNMTLVTLLVEN 223


>GPU:gi|3986159|gnl|PID|d1035925 (AB015231) VR1sk [Mus musculus]
           Length = 563

 Score = 299 (138.8 bits), Expect = 9.8e-136, Sum P(6) = 9.8e-136
 Identities = 69/175 (39%), Positives = 94/175 (53%)

Query:   391 FFLNFLCNLIYMFIFTAVAYHQPTLKKAAPHLKAEVGNSMLLTGHILILLGGIYLLVGQL 450
             F+ NF    +YM IFTA AY++P         LK  VG+    +TG IL +          +
Sbjct:   127 FYFNFFVYCLYMIIFTAAAYYRPVEGLPPYKLKNTVGDYFRVTGEILSVXXXXXXXXXRGI 186

Query:   451 WYFWRRHVFIWISFIDSYFEILFLFQALLKPVSQVLCFLAIEWYLPLLVSALVLGWLNLL 510
              YF +R    +   F+DSY EILF  Q+L   VS VL F   + Y+  +V +L  +GW N+L
Sbjct:   187 QYFLQRRPSLKSLFVDSYSEILFFVQSLFMLVSVVLYFSQRKEYVASMVFSLAMGWTNML 246

Query:   511 YYTRGFQHTGIYSVMIQKVILRDLLRFLLIYLVFLFGFAVALVSLSQEAWRPEAP 565
             YYTRGFQ  GIY+VMI+K+ILRDL R                A+V+L ++      P
Sbjct:   247 YYTRGFQQMGIYAVMIEKMILRDLCRXXXXXXXXXXXXXTAVVTLIEDGKNNSLP 301

 Score = 253 (117.5 bits), Expect = 9.8e-136, Sum P(6) = 9.8e-136
 Identities = 50/89 (56%), Positives = 64/89 (71%)

Query:   586 GAQYRGILEASLELFKFTIGMGELAFQEQLHFRGMVLLLLLAYVLLTYILLLNMLIALMS 645
             G  Y  +    LELFKFTIGMG+L F E   F+ + ++LLLAYV+LTYILLLNMLIALM
Sbjct:   317 GNSYNSLYSTCLELFKFTIGMGDLEFTENYDFKAVFIILLLAYVILTYILLLNMLIALMG 376

Query:   646 ETVNSVATDSWSIWKLQKAISVLEMENGY 674
             ETV  V+ +S  IWKLQ A ++L++E  +
Sbjct:   377 ETVGQVSKESKHIWKLQWATTILDIERSF 405

 Score = 163 (75.7 bits), Expect = 9.8e-136, Sum P(6) = 9.8e-136
 Identities = 28/47 (59%), Positives = 34/47 (72%)

Query:   678 RKKQRAGVMLTVGTKPDGSPDERWCFRVEEVNWASWEQTLPTLCEDP 724
             RK  R+G M+TVG    DG+PD RWCFRV+EVNW+ W Q L  + EDP
Sbjct:   410 RKAFRSGEMVTVGKSSDGTPDRRWCFRVDEVNWSHWNQNLGIINEDP 456

 Score = 162 (75.2 bits), Expect = 9.8e-136, Sum P(6) = 9.8e-136
 Identities = 28/38 (73%), Positives = 34/38 (89%)

Query:   323 HLSRKFTEWCYGPVRVSLYDLASVDSCEENSVLEIIAF 360
             HLSRKFTEW YGPV  SLYDL+ +D+CE+NSVLE+IA+
Sbjct:    57 HLSRKFTEWAYGPVHSSLYDLSCIDTCEKNSVLEVIAY 94

 Score = 129 (59.9 bits), Expect = 9.8e-136, Sum P(6) = 9.8e-136
 Identities = 27/49 (55%), Positives = 36/49 (73%)

Query:   269 MYDGLLQAGARLCPTVQLEDIRNLQDLTPLKLAAKEGKIEIFRHILQRE 317
             MY+ +L  GA+L PT++LE+I N + LTPL LAA  GKI +  +ILQRE
Sbjct:     1 MYNEILILGAKLHPTLKLEEITNRKGLTPLALAASSGKIGVLAYILQRE 49

 Score = 94 (43.6 bits), Expect = 9.8e-136, Sum P(6) = 9.8e-136
 Identities = 15/30 (50%), Positives = 24/30 (80%)

Query:   363 KSPHRHRMVVLEPLNKLLQAKWDLLIPKFF 392
```

```
            ++P+RH M+++EPLN+LLQ KWD  + + F
Sbjct:    98 ETPNRHDMLLVEPLNRLLQDKWDRFVKRIF 127
```

Score = 46 (21.4 bits), Expect = 2.3e-77, Sum P(5) = 2.3e-77
Identities = 11/48 (22%), Positives = 24/48 (50%)

```
Query:   435 HILILLGGIYLLVGQLWYFWRRHVFIWISFIDSYFEILFLFQALLKPV 482
            H ++L+  +  L+   W  + + +F +  F+   + I+F   A  +PV
Sbjct:   103 HDMLLVEPLNRLLQDKWDRFVKRIFYFNFFVYCLYMIIFTAAAYYRPV 150
```

Score = 42 (19.5 bits), Expect = 1.2e-122, Sum P(6) = 1.2e-122
Identities = 9/22 (40%), Positives = 16/22 (72%)

```
Query:   209 GELPLSLAACTKQWDVVSYLLE 230
            G  PL+LAA + +  V++Y+L+
Sbjct:    26 GLTPLALAASSGKIGVLAYILQ 47
```

```
>GP:gi|2911863 (AF047660) contains similarity to ankyrin repeats
          [Caenorhabditis elegans]
          Length = 900
```

Score = 103 (47.8 bits), Expect = 6.5e-20, Sum P(8) = 6.5e-20
Identities = 23/89 (25%), Positives = 44/89 (49%)

```
Query:   497 LLVSALVLGWLNLLYYTRGFQHTGIYSVMIQKVILRDLLRFLLIYLVFLFGFAVALVSLS 556
            L+   ++   ++ LYY R  +  G + +M+  +I  D+ RF+LIY +FL GF+ +   +
Sbjct:   592 LITVTMIFTTVHYLYYCRVIRFVGPFVLMVYTIIATDIFRFMLIYGIFLMGFSQSFSLIF 651

Query:   557 QEAWRPEAPTGPNATESVQPMEGQEDEGN 585
                R          T+  +  EG +++ N
Sbjct:   652 LSCEREANVIKKLITDQSEASEGSDNKFN 680
```

Score = 63 (29.3 bits), Expect = 6.5e-20, Sum P(8) = 6.5e-20
Identities = 15/27 (55%), Positives = 18/27 (66%)

```
Query:   291 NLQDLTPLKLAAKEGKIEIFRHILQRE 317
            N Q L+PL LAAK  K E+F  IL+ E
Sbjct:   328 NKQSLSPLTLAAKLAKKEMFDEILELE 354
```

Score = 56 (26.0 bits), Expect = 6.5e-20, Sum P(8) = 6.5e-20
Identities = 16/48 (33%), Positives = 25/48 (52%)

```
Query:   151 LVNAQCTDDYYRGHSALHIAIEKRSLQCVKLLVENGANVHARACGRFF 198
            L+N      + + G S LH AI      + V    ++ GA+V++R  G FF
Sbjct:   185 LLNDIHISEDFYGLSPLHQAIINTDCKLVYKFLKLGADVNSRCYGAFF 232
```

Score = 54 (25.1 bits), Expect = 6.5e-20, Sum P(8) = 6.5e-20
Identities = 12/23 (52%), Positives = 13/23 (56%)

```
Query:   207 YFGELPLSLAACTKQWDVVSYLL 229
            Y GE PLS AAC  Q +     LL
Sbjct:   263 YLGEYPLSFAACLNQPESFRLLL 285
```

Score = 49 (22.8 bits), Expect = 6.5e-20, Sum P(8) = 6.5e-20
Identities = 8/23 (34%), Positives = 12/23 (52%)

```
Query:   331 WCYGPVRVSLYDLASVDSCEENS 353
            W YG     + Y LA +D+   E +
Sbjct:   359 WAYGDASSTAYPLAKIDTINETT 381
```

Score = 47 (21.8 bits), Expect = 6.5e-20, Sum P(8) = 6.5e-20
Identities = 11/30 (36%), Positives = 18/30 (60%)

```
Query:   236 ASLQATDSQGNTVLHALVMISDNSAENIAL 265
             A+  A D+ GN+VLH  V+  + +   +AL
Sbjct:   289 ANPNAQDTNGNSVLHMCVIHENMAMFKLAL 318

 Score = 46 (21.4 bits), Expect = 5.7e-13, Sum P(6) = 5.7e-13
 Identities = 9/27 (33%), Positives = 17/27 (62%)

Query:   163 GHSALHIAIEKRSLQCVKLLVENGANV 189
             G+S LH+ +   ++   KL +E GA++
Sbjct:   298 GNSVLHMCVIHENMAMFKLALECGASL 324

 Score = 43 (20.0 bits), Expect = 6.5e-20, Sum P(8) = 6.5e-20
 Identities = 8/18 (44%), Positives = 13/18 (72%)

Query:   634 ILLLNMLIALMSETVNSV 651
             I+  NMLIA+M+ T  ++
Sbjct:   753 IMQFNMLIAMMTRTYETI 770

 Score = 41 (19.0 bits), Expect = 6.5e-20, Sum P(8) = 6.5e-20
 Identities = 10/27 (37%), Positives = 16/27 (59%)

Query:   113 GSTGKTCLMKAVLNLKDGVNACILPLL 139
             GS G+T +   +L+  D  NA +L +L
Sbjct:   153 GSMGETIIGCCLLHASDIHNALVLKIL 179

 Score = 35 (16.3 bits), Expect = 0.00016, Sum P(3) = 0.00016
 Identities = 9/37 (24%), Positives = 16/37 (43%)

Query:    67 SQPDPNRFDRDRLFNAVSRGVPEDLAGLPEYLSKTSK 103
             S+P P R+ ++      V   +     GL E+    S+
Sbjct:   464 SEPFPGRYGKNSTLQQVKPVINATSRGLVEWSEPLSQ 500

 Score = 34 (15.8 bits), Expect = 6.8e-11, Sum P(8) = 6.8e-11
 Identities = 8/31 (25%), Positives = 17/31 (54%)

Query:   422 LKAEVGNSMLLTGHILILLGGIYLLVGQLWY 452
             L  ++   +L+  ++LI +  I+  V  L+Y
Sbjct:   577 LACDLSPVLLVVDNVLITVTMIFTTVHYLYY 607


>GP:gi|3875319|gnl|PID|e1344970 (Z74030) similar to ankyrin repeats
            [Caenorhabditis elegans] >GP:gi|3876480|gnl|PID|e1346172 (Z72508)
            similar to ankyrin repeats [Caenorhabditis elegans]
            Length = 790

 Score = 97 (45.0 bits), Expect = 1.1e-19, Sum P(7) = 1.1e-19
 Identities = 18/53 (33%), Positives = 32/53 (60%)

Query:   497 LLVSALVLGWLNLLYYTRGFQHTGIYSVMIQKVILRDLLRFLLIYLVFLFGFA 549
             + + +++L   + LYY R     G + +M+  +I  DL+RF +IY +FL GF+
Sbjct:   526 MAIISILLVTQHFLYYMRAIPFVGPFVLMVYTIIATDLVRFAMIYSIFLVGFS 578

 Score = 89 (41.3 bits), Expect = 1.1e-19, Sum P(7) = 1.1e-19
 Identities = 19/48 (39%), Positives = 27/48 (56%)

Query:   151 LVNAQCTDDYYRGHSALHIAIEKRSLQCVKLLVENGANVHARACGRFF 198
             L+N  C  + Y G S LH+AI  +  Q   LL+  GA+++ R  G FF
Sbjct:   189 LINDICVSEEYYGLSPLHLAIVNQDAQFTSLLLRLGADLNQRCYGAFF 236

 Score = 62 (28.8 bits), Expect = 1.1e-19, Sum P(7) = 1.1e-19
 Identities = 13/23 (56%), Positives = 14/23 (60%)
```

```
Query:   207 YFGELPLSLAACTKQWDVVSYLL 229
             YFGE PLS A C  Q D+   LL
Sbjct:   267 YFGEYPLSFAICMGQHDLFRMLL 289

 Score = 51 (23.7 bits), Expect = 1.1e-19, Sum P(7) = 1.1e-19
 Identities = 10/19 (52%), Positives = 13/19 (68%)

Query:   236 ASLQATDSQGNTVLHALVM 254
             A+L A D+ GNT LH  V+
Sbjct:   293 ANLSAQDTNGNTALHLCVI 311

 Score = 49 (22.8 bits), Expect = 1.1e-19, Sum P(7) = 1.1e-19
 Identities = 11/51 (21%), Positives = 27/51 (52%)

Query:   601 KFTIGMGELAFQEQLHFRGMVLLLLLAYVLLTYILLLNMLIALMSETVNSV 651
             +F++   E++  +    + +  L+ + +      IL  N+LIA+M+ T  ++
Sbjct:   626 EFSVLYREMSACDNFWMKWIGKLIFVIFETVSILQFNLLIAMMTRTYETI 676

 Score = 43 (20.0 bits), Expect = 1.2e-06, Sum P(5) = 1.2e-06
 Identities = 7/27 (25%), Positives = 16/27 (59%)

Query:   163 GHSALHIAIEKRSLQCVKLLVENGANV 189
             G++ALH+ +    +  +  ++E G N+
Sbjct:   302 GNTALHLCVIHDKMDMLDAVLEAGGNI 328

 Score = 39 (18.1 bits), Expect = 5.5e-12, Sum P(7) = 5.5e-12
 Identities = 12/56 (21%), Positives = 25/56 (44%)

Query:   461 WISFIDSYFEILFLFQALLKPVSQVLCFLAIEWYLPLLVSALVLGWLNLLYYTRGF 516
             W +F+ ++   L    A L  +  + C LA  ++   L     +  +++L  T+ F
Sbjct:   483 WFNFLKAFPAKLMFKGAFLFIIISIPCRLACSFHEFFLTIDNTMAIISILLVTQHF 538

 Score = 38 (17.6 bits), Expect = 1.1e-19, Sum P(7) = 1.1e-19
 Identities = 9/18 (50%), Positives = 12/18 (66%)

Query:   289 IRNLQDLTPLKLAAKEGK 306
             + N Q+LT L LAA+  K
Sbjct:   330 LANKQNLTALTLAARLAK 347

 Score = 37 (17.2 bits), Expect = 4.7e-18, Sum P(7) = 4.7e-18
 Identities = 7/15 (46%), Positives = 9/15 (60%)

Query:   723 DPSGAGVPRTLENPV 737
             DP G+     +ENPV
Sbjct:   599 DPMGSEFNNIMENPV 613

 Score = 36 (16.7 bits), Expect = 1.1e-19, Sum P(7) = 1.1e-19
 Identities = 10/47 (21%), Positives = 16/47 (34%)

Query:   376 LNKLLQAKWDLLIPKFFLNFLCNLIYMFIFTAVAYHQPTLKKAAPHL 422
             + ++L  KW       +L  L   I+ +     AY          HL
Sbjct:   362 IEQILDEKWKAYGRALWLRSLLGFIFFYCCFVCAYMLRPSSATTEHL 408

 Score = 35 (16.3 bits), Expect = 3.0e-08, Sum P(6) = 3.0e-08
 Identities = 9/23 (39%), Positives = 11/23 (47%)

Query:   207 YFGELPLSLAACTKQWDVVSYLL 229
             Y+G  PL LA   +     S LL
Sbjct:   199 YYGLSPLHLAIVNQDAQFTSLLL 221

 Score = 34 (15.8 bits), Expect = 3.9e-12, Sum P(5) = 3.9e-12
 Identities = 7/21 (33%), Positives = 13/21 (61%)
```

```
Query:   297 PLKLAAKEGKIEIFRHILQRE 317
             PL  A   G+ ++FR +L ++
Sbjct:   272 PLSFAICMGQHDLFRMLLAKK 292

 Score = 34 (15.8 bits), Expect = 8.9e-10, Sum P(7) = 8.9e-10
 Identities = 6/18 (33%), Positives = 12/18 (66%)

Query:   610 AFQEQLHFRGMVLLLLLA 627
             AF  +L F+G  L ++++
Sbjct:   489 AFPAKLMFKGAFLFIIIS 506

 Score = 34 (15.8 bits), Expect = 4.0e-08, Sum P(6) = 4.0e-08
 Identities = 11/40 (27%), Positives = 16/40 (40%)

Query:   153 NAQCTDDYYRGHSALHIAIEKRSLQCVKLLVENGANVHAR 192
             N   T   Y G   L  AI         ++L+   AN+ A+
Sbjct:   259 NTNYTGSMYFGEYPLSFAICMGQHDLFRMLLAKKANLSAQ 298


>GP:gi|2642590 (AF031408) olfactory channel [Caenorhabditis elegans]
           Length = 937

 Score = 93 (43.2 bits), Expect = 6.8e-16, Sum P(5) = 6.8e-16
 Identities = 19/36 (52%), Positives = 25/36 (69%)

Query:   163 GHSALHIAIEKRSLQCVKLLVENGANVHARACGRFF 198
             G SALH+AI     + V LL+ + A+V+ARACG FF
Sbjct:   172 GQSALHLAIVHDDYETVSLLLNSKADVNARACGNFF 207

 Score = 92 (42.7 bits), Expect = 6.8e-16, Sum P(5) = 6.8e-16
 Identities = 20/53 (37%), Positives = 31/53 (58%)

Query:   497 LLVSALVLGWLNLLYYTRGFQHTGIYSVMIQKVILRDLLRFLLIYLVFLFGFA 549
             L V AL   W+ LL++ R  + TG +  MI  +I  D++RF +I  +FL  F+
Sbjct:   500 LFVFALPGSWIFLLFFARSAKLTGPFVQMIYSMIAGDMIRFAIISAIFLVSFS 552

 Score = 57 (26.5 bits), Expect = 6.8e-16, Sum P(5) = 6.8e-16
 Identities = 10/24 (41%), Positives = 15/24 (62%)

Query:   207 YFGELPLSLAACTKQWDVVSYLLE 230
             Y+GE PL+ AAC     D+   L++
Sbjct:   226 YYGEYPLAFAACFGNKDIYDLLIQ 249

 Score = 50 (23.2 bits), Expect = 6.8e-16, Sum P(5) = 6.8e-16
 Identities = 11/25 (44%), Positives = 15/25 (60%)

Query:   291 NLQDLTPLKLAAKEGKIEIFRHILQ 315
             N    TPL LA K G+ +IF  +L+
Sbjct:   294 NHAGFTPLTLATKLGRKQIFEEMLE 318

 Score = 44 (20.4 bits), Expect = 6.8e-16, Sum P(5) = 6.8e-16
 Identities = 10/24 (41%), Positives = 15/24 (62%)

Query:   242 DSQGNTVLHALVMISDNSAENIAL 265
             DS GNT+LH  V+   +S  + A+
Sbjct:   258 DSFGNTILHMCVINYSSSMYSYAV 281

 Score = 37 (17.2 bits), Expect = 2.2e-05, Sum P(4) = 2.2e-05
 Identities = 9/24 (37%), Positives = 13/24 (54%)

Query:   208 FGELPLSLAACTKQWDVVSYLLEN 231
             FG+  L LA     ++ VS LL +
Sbjct:   171 FGQSALHLAIVHDDYETVSLLLNS 194
```

```
 Score = 34 (15.8 bits), Expect = 3.6e-16, Sum P(6) = 3.6e-16
 Identities = 7/21 (33%), Positives = 11/21 (52%)

Query:   364 SPHRHRMVVLEPLNKLLQAKW 384
             +P    M+  E + +LL  KW
Sbjct:   363 TPEHLDMIGSEVIQRLLADKW 383


>GP:gi|2854148 (AF045639) contains similarity to ankyrin repeats
            [Caenorhabditis elegans]
            Length = 957

 Score = 93 (43.2 bits), Expect = 7.6e-16, Sum P(5) = 7.6e-16
 Identities = 19/36 (52%), Positives = 25/36 (69%)

Query:   163 GHSALHIAIEKRSLQCVKLLVENGANVHARACGRFF 198
             G SALH+AI      + V LL+ + A+V+ARACG FF
Sbjct:   175 GQSALHLAIVHDDYETVSLLLNSKADVNARACGNFF 210

 Score = 92 (42.7 bits), Expect = 7.6e-16, Sum P(5) = 7.6e-16
 Identities = 20/53 (37%), Positives = 31/53 (58%)

Query:   497 LLVSALVLGWLNLLYYTRGFQHTGIYSVMIQKVILRDLLRFLLIYLVFLFGFA 549
             L V AL   W+ LL++ R  + TG +  MI  +I  D++RF +I  +FL  F+
Sbjct:   503 LFVFALPGSWIFLLFFARSAKLTGPFVQMIYSMIAGDMIRFAIISAIFLVSFS 555

 Score = 57 (26.5 bits), Expect = 7.6e-16, Sum P(5) = 7.6e-16
 Identities = 10/24 (41%), Positives = 15/24 (62%)

Query:   207 YFGELPLSLAACTKQWDVVSYLLE 230
             Y+GE PL+ AAC     D+   L++
Sbjct:   229 YYGEYPLAFAACFGNKDIYDLLIQ 252

 Score = 50 (23.2 bits), Expect = 7.6e-16, Sum P(5) = 7.6e-16
 Identities = 11/25 (44%), Positives = 15/25 (60%)

Query:   291 NLQDLTPLKLAAKEGKIEIFRHILQ 315
             N    TPL LA K G+ +IF  +L+
Sbjct:   297 NHAGFTPLTLATKLGRKQIFEEMLE 321

 Score = 44 (20.4 bits), Expect = 7.6e-16, Sum P(5) = 7.6e-16
 Identities = 10/24 (41%), Positives = 15/24 (62%)

Query:   242 DSQGNTVLHALVMISDNSAENIAL 265
             DS GNT+LH  V+   +S  + A+
Sbjct:   261 DSFGNTILHMCVINYSSSMYSYAV 284

 Score = 37 (17.2 bits), Expect = 2.4e-05, Sum P(4) = 2.4e-05
 Identities = 9/24 (37%), Positives = 13/24 (54%)

Query:   208 FGELPLSLAACTKQWDVVSYLLEN 231
             FG+  L LA      ++ VS LL +
Sbjct:   174 FGQSALHLAIVHDDYETVSLLLNS 197

 Score = 34 (15.8 bits), Expect = 4.1e-16, Sum P(6) = 4.1e-16
 Identities = 7/21 (33%), Positives = 11/21 (52%)

Query:   364 SPHRHRMVVLEPLNKLLQAKW 384
             +P    M+  E + +LL  KW
Sbjct:   366 TPEHLDMIGSEVIQRLLADKW 386
```

```
>GP:gi|3879753|gnl|PID|e1349345 (Z72514) Similarity to Human ankyrin
            (SW:ANK1_HUMAN) [Caenorhabditis elegans]
            Length = 519

 Score = 73 (33.9 bits), Expect = 3.6e-11, Sum P(6) = 3.6e-11
 Identities = 17/36 (47%), Positives = 19/36 (52%)

Query:   163 GHSALHIAIEKRSLQCVKLLVENGANVHARACGRFF 198
             G S LH AI     L+ V  L   GA+VH R  G FF
Sbjct:   186 GLSPLHQAIVNEDLEMVYFLCRKGADVHQRCYGSFF 221

 Score = 63 (29.3 bits), Expect = 3.6e-11, Sum P(6) = 3.6e-11
 Identities = 12/17 (70%), Positives = 13/17 (76%)

Query:   207 YFGELPLSLAACTKQWD 223
             Y+GE PLS AACT Q D
Sbjct:   252 YWGEYPLSFAACTNQVD 268

 Score = 52 (24.1 bits), Expect = 3.6e-11, Sum P(6) = 3.6e-11
 Identities = 13/27 (48%), Positives = 17/27 (62%)

Query:   289 IRNLQDLTPLKLAAKEGKIEIFRHILQ 315
             +RN   LTPL LAA+  K  I+  IL+
Sbjct:   315 VRNNLKLTPLALAARLAKKHIYDLILE 341

 Score = 51 (23.7 bits), Expect = 3.6e-11, Sum P(6) = 3.6e-11
 Identities = 10/22 (45%), Positives = 12/22 (54%)

Query:   331 WCYGPVRVSLYDLASVDSCEEN 352
             W YGPV    Y L  VD+  E+
Sbjct:   348 WRYGPVVCKAYPLNDVDTINES 369

 Score = 43 (20.0 bits), Expect = 3.6e-11, Sum P(6) = 3.6e-11
 Identities = 8/13 (61%), Positives = 10/13 (76%)

Query:   242 DSQGNTVLHALVM 254
             D+ GNTVLH  V+
Sbjct:   284 DTNGNTVLHLTVI 296

 Score = 37 (17.2 bits), Expect = 3.6e-11, Sum P(6) = 3.6e-11
 Identities = 8/35 (22%), Positives = 16/35 (45%)

Query:   376 LNKLLQAKWDLLIPKFFLNFLCNLIYMFIF[illegible]VAY 410
             + ++L++KW+    K     L   IY      +A+
Sbjct:   398 IEEVLESKWETFGKKQLFMSLAGYIYFLAVFYLAF 432


>GP:gi|3287188|gnl|PID|e315126 (Y10601) ankyrin-like protein [Homo sapiens]
            Length = 1119

 Score = 71 (33.0 bits), Expect = 2.7e-08, Sum P(6) = 2.7e-08
 Identities = 13/30 (43%), Positives = 20/30 (66%)

Query:   163 GHSALHIAIEKRSLQCVKLLVENGANVHAR 192
             G++ LH A+EK  ++ VK L+  GAN + R
Sbjct:    98 GNTPLHCAVEKNQIESVKFLLSRGANPNLR 127

 Score = 63 (29.3 bits), Expect = 2.7e-08, Sum P(6) = 2.7e-08
 Identities = 10/30 (33%), Positives = 20/30 (66%)

Query:   501 ALVLGWLNLLYYTRGFQHTGIYSVMIQKVI 530
             A+   W+N L Y + F++ GI+ VM++ ++
Sbjct:   838 AVYFYWMNFLLYLQRFENCGIFIVMLEVIL 867
```

```
 Score = 59 (27.4 bits), Expect = 9.0e-07, Sum P(6) = 9.0e-07
 Identities = 10/30 (33%), Positives = 19/30 (63%)

Query:   167 LHIAIEKRSLQCVKLLVENGANVHARACGR 196
             LH+A++   L+ +K+ ++NGA +     GR
Sbjct:   243 LHLAVQNGDLEMIKMCLDNGAQIDPVEKGR 272

 Score = 50 (23.2 bits), Expect = 2.7e-08, Sum P(6) = 2.7e-08
 Identities = 10/26 (38%), Positives = 18/26 (69%)

Query:   291 NLQDLTPLKLAAKEGKIEIFRHILQR 316
             +L  +TPL LAAK G  ++ + +L++
Sbjct:   479 DLHGMTPLHLAAKNGHDKVVQLLLKK 504

 Score = 49 (22.8 bits), Expect = 2.7e-08, Sum P(6) = 2.7e-08
 Identities = 10/26 (38%), Positives = 14/26 (53%)

Query:   209 GELPLSLAACTKQWDVVSYLLENPHQ 234
             G  PL LA  +  W++V+ LL    Q
Sbjct:   342 GRSPLILATASASWNIVNLLLSKGAQ 367

 Score = 48 (22.3 bits), Expect = 3.2e-05, Sum P(5) = 3.2e-05
 Identities = 9/32 (28%), Positives = 20/32 (62%)

Query:   524 VMIQKVILRDLLRFLLIYLVFLFGFAVALVSL 555
             +++ +VIL+ LLR  ++++  L  F ++   L
Sbjct:   860 IVMLEVILKTLLRSTVVFIFLLLAFGLSFYIL 891

 Score = 41 (19.0 bits), Expect = 2.7e-08, Sum P(6) = 2.7e-08
 Identities = 9/28 (32%), Positives = 15/28 (53%)

Query:   525 MIQKVILRDLLRFLLIYLVFLFGFAVAL 552
             +I K +LR  + F+ + L F   F + L
Sbjct:   865 VILKTLLRSTVVFIFLLLAFGLSFYILL 892

 Score = 40 (18.6 bits), Expect = 2.9e-07, Sum P(5) = 2.9e-07
 Identities = 13/50 (26%), Positives = 24/50 (48%)

Query:   620 MVLLLLLAYVLLTYILLLNMLIALMSETVNSVATDSWSIWKLQKAISVLE 669
             +V + LL    L++ +LLN+     S  ++ + T S  +  +    S LE
Sbjct:   875 VVFIFLLLAFGLSFYILLNLQDPFSSPLLSIIQTFSMMLGDINYRESFLE 924

 Score = 40 (18.6 bits), Expect = 7.6e-05, Sum P(5) = 7.6e-05
 Identities = 8/19 (42%), Positives = 12/19 (63%)

Query:   296 TPLKLAAKEGKIEIFRHIL 314
             TPL LA + G +E+ +  L
Sbjct:   241 TPLHLAVQNGDLEMIKMCL 259

 Score = 39 (18.1 bits), Expect = 2.7e-08, Sum P(6) = 2.7e-08
 Identities = 7/19 (36%), Positives = 14/19 (73%)

Query:   625 LLAYVLLTYILLLNMLIAL 643
             L+++ +   I+L+N+LI L
Sbjct:   941 LVSFTIFVPIVLMNLLIGL 959

 Score = 39 (18.1 bits), Expect = 6.8e-07, Sum P(6) = 6.8e-07
 Identities = 9/36 (25%), Positives = 18/36 (50%)

Query:   293 QDLTPLKLAAKEGKIEIFRHILQREFSGLSHLSRKF 328
             + LT L   +  +IE+  H + +E+  +  L+  F
Sbjct:   681 EPLTALNAMVQNNRIELLNHPVCKEYLLMKWLAYGF 716
```

Exhibit D

Qualified Target Summary Sheet

	Vanilloid Receptor Homologue (VR-2)
CFA Disease Area (s):	Pain
Druggable Target Class:	Calcium channel
MPI Gene Sequence Identifier:	Flh21e11 (Mine 18560)
Top Blast Hit:	Rat vanilloid receptor 1 (VR1)
Amino Acid Coding Region:	ORF: 361-2652
CDNA Length:	2806 bp
Source (Tissue / Cell Line):	First clone identified in an internal heart library
Novel / Unrecognized:	? Unrecognized / Novel
% Novelty:	66% novel across the complete cDNA. Hits unannotated sequence in Non-Public Patent Data Base
Patent Status:	Filed Nov. 1, 1998
Full Length Clone:	Yes
Expression Profiling Results:	Present in a sub-population of sensory neurons different from VR1. Also present in sympathetic neurons.
Background:	The published vanilloid receptor (Caterina et. Al. Nature 389:816-24, 1997) responds to heat and capsaicin by activating Ca++ influx in sensory neurons (Tominaga et.al., Neuron 21: 531-43, 1998). Capsaicin also binds to this channel.
Hypothesis:	This channel may be responsible for hypersensitivity in chronic neuropathic pain and represents a unique target for pain.
Assay Type:	Cell-based assay
Reagents Needed:	Open reading frame will be cloned by Millennium into pCDNA 3.1
Readout:	
Critical Experiments Necessary:	

MPI Target Name:	Vanilloid Receptor Homologue (VR-2)
QT Nomination Date:	12/22/98
Acti n Tak n:	Accepted QT (unrecognized) Pending full length cDNA
Date Accepted:	
Bay r QT Leader:	
MPI QT Leader:	Rory Curtis or Peter DiStefano